

## REMARKS

Claim 26 has been amended to more succinctly claim the invention.

### **CLAIM REJECTIONS UNDER 35 U.S.C. §§102, 103**

The Examiner has rejected claims 26 – 32 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Builder et al., U.S. Patent number 5407810 in view of Rudolph, R. Renaturation of Recombinant, Disulfide Bonded Proteins from "Inclusion Bodies", Modern Methods in Protein and Nucleic Acid Res. 1990 (hereafter referred to as Rudolph).

The Examiner indicates that he believes that the Applicant's use in the claims of the transitional phrase "consisting essentially of" limits the scope of a claim to the specified material or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. However, the Examiner furthers states that because the Applicant has also used, in claim 1, the term "comprising" prior to the use of the phrase "consisting essentially of" that the scope of the novel characteristics of the presently claimed invention includes the additional elements in the invention of Builder, et al.

The Applicant respectfully disagrees with the Examiner since the refolding method contemplated by Builder in claim 25 (claim 1 does not claim a refolding method but an isolation method) clearly includes the use of "about 0.2 to 3M of an alkaline earth, alkali metal, or ammonium salt, about 0.1 to 9M of a chaotropic agent, and about 0.01 to 15 uM of a copper or manganese salt." The Applicant has intended that the present method comprise a treatment of a monomeric TGF- $\beta$  protein in a refolding buffer which buffer consists essentially of glutathione in its reduced form and an organic solvent which is DMSO (Dimethylsulfoxide) or DMF (Dimethylformamide) or a mixture of DMSO and DMF. As such, the Applicant's invention does not include the additional elements of Builder. The Applicant has amended claim 26 to more succinctly define what aspects of the method may be characterized as "comprising" versus "consisting essentially of" so that there is no unintended overlap of the scope of these terms with respect to the elements of the present invention that they characterize.

The Examiner further states that "the basic and novel characteristics of the invention is the same as that taught by Builder because no evidence has been offered that the additional ingredients in the buffer used in Builder's process affect the basic and novel characteristics of the claimed invention." The Applicant agrees that the use of the phrase "consisting essentially

of" creates some limit to the scope of a claim to materials that do not affect a material change in the basic and novel characteristics of a claimed invention. The Applicant has stated in page 4 line 4-7 that chaotropic agents were unsuccessful with TGF- $\beta$ . The Builder reference teaches that chaotropic agents are required in the process described therein and therefore teaches away from the determinations made by the Applicants. Thus there is no motivation to use the Applicants process in the Builder reference.

Rudolph indicates that disulfide bond reformation in denatured peptides may be achieved with glutathione but does not attribute renaturation to the use of glutathione alone. Rudolph merely contemplates disulfide bond reformation in peptides through several alternative methods (see page 161 line 9). Rudolph does not teach which process works with a specific type of peptide or class of peptides such as TGF- $\beta$ . In fact, Rudolph also contemplates that certain peptides may require regeneration of disulfide bonds after other chemical modifications such as by chaotropic agents, e.g. guanidinium chloride (see page 161 last paragraph and page 162). The appropriate conditions must be selected for each peptide is the message that can be gleaned from the teaching of Rudolph.

The example used in Rudolph is that of ribonuclease and the example in Builder is IGF-1. These peptides are not as complex as the structure of TGF- $\beta$ . TGF- $\beta$  has a very complicated 3D structure with two disulfide bridges forming a tight ring structure of eight residues and with a third disulfide bridge pointing directly through that ring. In view of this "special" character, there was no positive expectation, but in fact the contrary expectation, that TGF- $\beta$ s would not follow the folding behaviour of other proteins when subjected to any particular folding buffer.

For these reasons, the Applicants respectfully request that the Examiner withdraw the rejections of claims 26-32.

#### **OBVIOUSNESS-TYPE DOUBLE PATENTING rejection over Cerletti US 6,057,430**

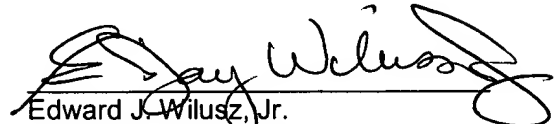
The Claims have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2,8-23 of US Patent 6 057 430. Applicant herein files a terminal disclaimer to disclaim the terminal part of the statutory term of any patent granted on this application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §154-156 and §173 as shortened by any terminal disclaimer filed prior to the grant of US Patent 6 057 430. The Examiner is respectfully requested to reconsider and withdraw this ground of rejection.

The Applicant believes that the case is in condition for allowance and respectfully requests early notice to that effect.

If it will advance prosecution of the case the Examiner is urged to contact the Applicant's attorney at the telephone number listed below.

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